Impact of the upper gut on body fluid regulation and blood pressure

– potential involvement of a locally expressed renin-angiotensin system

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ABSTRACT

This thesis explores the role of the upper gut in the regulation of diuresis and blood pressure control in relation to the novel finding of a mucosa-located renin-angiotensin system (RAS). RAS is a regulatory super-system vital for body fluid homeostasis and blood pressure control. Recent research demonstrates that RAS is not only an endocrine (blood borne) system, but also in all respects locally expressed influencing tissue growth and differentiation as well as inflammatory responses.

A first aim of the present thesis-project was to explore if RAS was expressed in the mucosa of the stomach and duodenum. Indeed, by use of western blot and immunohistochemistry most components of RAS were found in several compartments of the gastric mucosa of the Mongolian gerbil (model for human *Helicobacter pylori* infection) and also in the human mucosa. It was also observed that a subset of gastric mucosal endocrine cells expressed AT1 receptors suggesting that activity in a local RAS can influence enteroendocrine signalling. RAS components were found also in the mucosa of the human duodenum.

The second aim of the thesis was to examine the potential functionality of the local mucosal RAS described above. The project was focussed on a previously described sodium/volume sensor postulated to be situated in upper gut. Such a sensor is activated by food ingestion/drinking and increases renal diuresis already in the pre-absorptive state. The upper-gut location of this regulatory principle was demonstrated in healthy volunteers by intragastric instillation of 750 ml saline that almost promptly was followed by an increased diuresis, whereas intrajejunal instillation had an additional 60 min lag-time until response. In a second set of experiments, the volunteer were first exposed to gastric instillation of saline (with sham-intubation as time control) and after 30 to 40 min a gastroduodenoscopy with sampling of mucosal biopsies was performed. The tissue specimens were examined for RAS components and the principal finding was that the concentration of the pro-hormone angiotensinogen decreased in the duodenal mucosa, but not in the stomach. The results confirm that a volume sensor is located to the upper gut in man. Furthermore, local mucosal RAS, particularly in the duodenum, may be involved in mediating the diuresis occurring in the pre-absorptive state after drinking and eating.

The third aim of the project was related to the physiological and clinical relevance of the sodium/volume monitor described above. Patients participating in the Swedish Obese Subjects (SOS) study were investigated. Gastric bypass (GBP), meaning that food and drinks are led directly into the jejunum thus bypassing the major part of the stomach and duodenum, was compared to gastric band constructions. The latter type of weight reducing surgery restricts the food intake capacity with the alimentary route intact. Interestingly, after adjustments for weight loss the GBP patients exhibited a larger 24h diuresis and a markedly more reduced systolic and diastolic pressure than the gastric band patients. These changes were prominent also 10 years after surgical intervention and were not related to the reduced body weight. Furthermore, the GBP patients consumed, despite a lowered blood pressure, approximately 1 g dietary salt more per day than patients operated with the restrictive banding techniques. This picture is compatible with that the sodium/volume sensor induces diuresis in an anticipatory fashion in relation to ingestive load and also inhibits salt appetite. Upon removal of this pre-absorptive regulatory mechanisms (as following GBP), more rough post-absorptive regulatory principles dominate that very probably results in an overshooting diuretic effect with depressor action and an increased salt intake.

Key words: *angiotensin, stomach, duodenum, sodium, salt, diuresis, appetite, gastric bypass, blood pressure*

ISBN 978-91-628-8287-7 Gothenburg 2011

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Akademisk avhandling

som för avläggande av doktorsexamen vid Sahlgrenska akademin
vid Göteborgs universitet kommer att offentligen försvaras i Kammaren,
Vita stråket 12, Sahlgrenska Universitetssjukhuset,
Göteborg, fredagen den 10 juni kl. 13.00

av

Peter Hallersund
Examinerad läkare

Fakultetsopponent:
Professor Per Hellström
Uppsala universitet, Uppsala

Avhandlingen baseras på följande arbeten:

I. Hallersund P, Helander HF, Casselbrant A, Edebo A, Fändriks L, Elfvin A. Angiotensin II receptor expression and relation to Helicobacter pylori-infection in the stomach of the Mongolian gerbil. *BMC Gastroenterol*. 2010 Jan 14;10:3

II. Hallersund P, Elfvin A, Helander HF, Fändriks L. The expression of renin-angiotensin system components in the human gastric mucosa. *J Renin Angiotensin Aldosterone Syst.* 2011 Mar 12;54-64. Epub 2010 Aug

III. Hallersund, P, Edebo A, Casselbrant A, Spak E, Fändriks L. The sodium/volume sensor in the upper gut in man – potential involvement of a local renin-angiotensin system. *In manuscript*

IV. Hallersund P, Sjöström L, Olbers T, Lönroth H, Jacobson P, Wallenius V, Näslund I, Carlsson LM, Fändriks L. Long-term effects on blood pressure and dietary salt intake by weight reducing surgery – an analysis of 10-year follow-up data from the Swedish Obese Subjects study. *In manuscript*

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